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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/462,993	04/17/00	KIENY	M 017753-122

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/462,993	KIENY ET AL.	
	Examiner	Art Unit	
	Michael Penn	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

The Examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Michael G. Penn, Art Unit 1633.

Claims 21-37, 39, and 40 are pending and under consideration in the instant office action.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 12 is acknowledged. Upon consideration of applicant's arguments, Group III will be examined in addition to Group I. Furthermore, the E6 and E7 sequence (SEQ ID NO: 1 and 2) will be examined.

With respect to the traversal concerning Group III, applicant argues that examination of this does not place an undue burden on the examiner. This is found persuasive because Group I and III are drawn to vectors encoding nucleic acids and methods of use of these as a vaccine. Groups I and III are examined herein and the remaining restriction requirement is deemed proper and is therefore made FINAL.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-37, 39, and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for treatment of cancer or a tumor in a subject by subcutaneous, intraperitoneal, intramuscular, or scarification delivery of a vaccinia vector encoding the HPV E6 or E7 proteins, and even actual prevention of tumors in mice, neither the specification or the state of the art reasonably provides enablement for the use of all vector systems, all routes of administration, or for this invention to prevent cancer in any subject. Furthermore, while enabling for the use of E6 and E7 proteins that have been mutated to prevent oncogenesis, the specification does not enable the use of all mutated forms of E6 and E7 proteins. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

While enabling for treatment of cancer or a tumor in a subject by subcutaneous, intraperitoneal, intramuscular, or scarification delivery of a vaccinia vector encoding the HPV E6 or E7 proteins, and even actual prevention of tumors in mice, neither the specification or the state of the art reasonably provides enablement for the use of all vector systems, all routes of administration, or for this invention to prevent cancer in any subject. Furthermore, while enabling for the use of E6 and E7 proteins that have been mutated to prevent oncogenesis, the specification does not enable the use of all mutated forms of E6 and E7 proteins.

The pending application is in the area of DNA vaccinations. At the time of application, and currently, the field of DNA vaccines was highly unpredictable, especially with regard to the use of predictive animal modeling.

The state of the art concerning extrapolation of animal study results to human subjects is exemplified by McCluskie et al. (Mol. Med., 5, pp. 287-300, 1999). McCluskie teaches that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in non-human primates," that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found only to be relatively so in chimpanzees..., and especially not at all in Aotus monkeys" and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice-versa" (p. 296, column 2, second and third paragraphs). In addition, McCluskie et al. teaches that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen" (p. 297, column 1).

Moreover, although progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the

experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The generation of an immune response that gives a therapeutic effect does not necessarily mean that it will grant full protection and prevention against the initial development of cervical cancer, or even subsequent challenges of cervical cancer. Vaccination of a patient who already has a

tumor burden is greatly different than vaccination of a tumor naïve subject. For example, the subject with tumor burden, in effect, provides additional and continual boosts of antigen, which could lead to a stronger response against the tumor, whereas the naïve subject relies completely on the vaccine to provide enough antigen to stimulate a vigorous immune response. Thus it is not apparent how one skilled in the art reasonably extrapolates, without undue experimentation, from the mouse model described in the specification to the full scope of the claimed invention. Moreover, in light of the state of the art concerning *in vivo* vector delivery, it is not apparent how the use of every vector system could be utilized by one skilled in the art, without undue experimentation. Particularly considering that the pending application is drawn to vaccinations, the choice of vector, especially viral vectors, could have a tremendous impact on the desired results. Different vector systems elicit different responses from the host immune system. At best, the specification and the state of the art enable administration of a vaccinia vector encoding E6 or E7 (or mutated forms of E6 or E7 that would eliminate oncogenesis) by scarification, subcutaneous, intraperitoneal, or intramuscular injection that would result in tumor regression of established tumors.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 24, 25, and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is vague and indefinite because it is unclear whether the polypeptide has a nuclear localization sequence. The claim refers to a polypeptide that "naturally has a nuclear location and is, in addition, deleted for its natural nuclear localization sequence." It is unclear whether this claim means that the polypeptide retains its nuclear localization without the nuclear localization sequence, or if the deletion of the nuclear localization sequence also eliminates nuclear retention. Clarification is necessary.

Claims 24 and 25 are vague and indefinite because they refer to the early and/or late region of the papillomavirus. It appears that the intent is to refer to regions of the papillomavirus *genome*. Clarification is necessary.

Claim 40 is vague and indefinite because the claim refers to a cancer or tumor as including a "papillomavirus infection" and a "low-grade cervical dysplasia." Having only a papillomavirus infection does not necessarily mean that there is cancer or a tumor. Furthermore, a low-grade cervical dysplasia is not necessarily a tumor. Although the claim also encompasses prevention of cancer or tumors, thus including papillomavirus infections and low-grade cervical dysplasias, clarification is necessary.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21, 22, 24-26, 34-37, 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al. (Lin et al., Cancer Research, Jan. 1, 1996, pp. 21-26).

Lin teaches a recombinant vaccinia vector encoding the open reading frame of the HPV-16 E7 antigenic peptide linked to the lysosome-associated membrane protein (LAMP-1) transmembrane domain and the LAMP-1 endoplasmic reticulum signal peptide so that E7 loses its nuclear retention capability (p.21. Lin further teaches delivery of this vector via intraperitoneal injection to treat TC-1 tumors (primary mouse lung cells transformed with HPV-16 E6 and E7, and *ras* oncogene) in mice and to prevent and treat HPV associated cervical malignancies (p. 22, 1st col. in materials and methods; p. 21 2nd col., 3rd paragraph).

The LAMP-1 transmembrane domain is equivalent to the limitation of a membrane anchoring sequence in claim 21 of the instant application because transmembrane domain and membrane anchoring sequence are both art accepted terms that refer to a series of hydrophobic amino acids that function to retain a protein in a cell membrane.

The E7 polypeptide is equivalent to the limitation in claim 21 of not naturally having a membrane location because E7 is normally retained within the nucleus of the cell, not in a membrane.

The limitation of claim 22 is met because using only the open reading frame of E7 does not include the nuclear localization sequence.

The limitations of claims 24-26 of the instant application are anticipated by Lin because E7 is an early region protein from the papillomavirus.

The limitation of using a poxvirus in claim 34 is anticipated by Lin because vaccinia is in the poxviridae family.

The limitation of claim 35 of using a phamaceutically acceptable carrier that allows administration by injection is anticipated by Lin because the vector was injected intraperitoneally.

The limitation of claims 39 and 40 of treating or preventing cancer, specifically cervical cancer, in a subject is anticipated by Lin because established tumors were treated by injection of their vaccinia vector and Lin teaches that this method would be used to treat or prevent HPV associated cervical malignancies.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21, 24-27, 34-37, and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (Lin et al., Cancer Research, Jan. 1, 1996, pp. 21-26) in view of Boursnell et al. (Boursnell et al., Vaccine, Nov. 1996, pp. 1485-94.

Lin teaches a recombinant vaccinia vector encoding the HPV-16 E7 antigenic peptide linked to the lysosome-associated membrane protein (LAMP-1) transmembrane domain and delivery of this vector via intraperitoneal injection to treat TC-1 tumors (primary mouse cells transformed with HPV-16 E6 and E7, and *ras* oncogene) in mice (p. 22, 1st col. in materials and methods). Lin does not teach the use of a vector encoding a nononcogenic variant of E6 or E7.

Boursnell teaches a recombinant vaccinia virus that encodes the HPV E6 and E7 for use in the treatment of cervical cancer. Boursnell further teaches site directed mutagenesis of the E7 coding sequences to eliminate Rb binding, thus rendering E7 as nontransforming. Moreover, Boursnell teaches that "...the presence of E6 and E7 proteins in cervical tumour cells offers an unusually clear cut opportunity for cancer immunotherapy, since they represent genuine tumour-specific antigens that could act as targets for destruction of tumour cells without damage to healthy host cells." (p. 1485, 2nd col., 2nd paragraph); however, that "...vaccination with the recombinant virus could lead to long term expression of E6 and E7 that could result in cell transformation..." and that although this potential risk of oncogenesis is low, mutating the E7 sequences creates a "...further margin of safety...." (p. 1489, 2nd col., last paragraph; p. 1490, 1st col., last paragraph).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the work of Lin with Boursnell to produce a recombinant vaccinia vector encoding a nononcogenic variant of E7 and a transmembrane domain. One of ordinary skill in the art would have been motivated to combine the teachings of Lin and Boursnell to create a safer immunotherapeutic vaccine for the treatment of cervical cancer.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 21, 24, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (Lin et al., Cancer Research, Jan. 1, 1996, pp. 21-26) in view of Jarrett et al. (Jarrett et al., Virology, 184, 1991, pp. 33-42).

Lin teaches a recombinant vaccinia vector encoding the HPV-16 E7 antigenic peptide linked to the lysosome-associated membrane protein (LAMP-1) transmembrane domain and delivery of this vector via intraperitoneal injection to treat TC-1 tumors (primary mouse cells transformed with HPV-16 E6 and E7, and *ras* oncogene) in mice (p. 22, 1st col. in materials and methods). Lin does not teach the use of a vector encoding a papillomavirus L1 or L2 polypeptide.

Jarrett teaches a plasmid vector encoding the papillomavirus open reading frames of both L1 and L2 for use in preparing peptide vaccines (p. 34, materials and methods). Jarrett does not teach the use of a membrane anchoring sequence in this vector.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the work of Lin with Jarrett to produce a recombinant vector encoding an L1 or L2 papillomavirus polypeptide that also contains a transmembrane domain. One of ordinary skill in the art would have been motivated to combine the teachings of Lin and Jarrett to produce a vector that encodes the L1 or L2 protein and a transmembrane domain so that the vector more efficiently presents the proteins to the immune system, thereby eliciting a more effective immune response.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 21, 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (Lin et al., Cancer Research, Jan. 1, 1996, pp. 21-26) in view of Chow et al. (McLaughlin et al., Cancer Res, May 15, 1996, pp. 2361-7), He et al. (Chow et al., J Virol, Jan. 1997, pp. 169-78), Kim et al. (Kim et al., J Immunol, Jan. 15, 1997, pp. 816-26), or Finke et al. (Finke et al., Gene Therapy, Jan. 1998, pp. 31-39).

Lin teaches a recombinant vaccinia vector encoding the HPV-16 E7 antigenic peptide linked to the lysosome-associated membrane protein (LAMP-1) transmembrane domain and delivery of this vector via intraperitoneal injection to treat TC-1 tumors (primary mouse cells transformed with HPV-16 E6 and E7, and *ras* oncogene) in mice (p. 22, 1st col. in materials and methods). Lin does not teach the use of a vector encoding a HPV E6 or E7 and an immunostimulator.

Chow teaches a bicistronic plasmid vector encoding a hepatitis-B antigen and interleukin-2 (IL-2) used to induce an immune response against hepatitis-B virus (p. 170, 1st column, 1st paragraph). Chow further teaches that this combination results in at least a 100-fold increase in the induction of both the humoral and cellular immune responses to the hepatitis-B antigen (p. 175, 1st paragraph of discussion). Chow does not teach the use of a membrane anchoring sequence in the vector.

He teaches bicistronic recombinant adenoviral and retroviral vectors encoding a hepatitis-B antigen and the B7-1 molecule (Figs. 1 and 2). He further teaches that the use of B7-1 could enhance the cytotoxic T lymphocyte response against antigens, and that this stronger T cell response is believed to be important to the clearance of viral infections (p. 122, 1st col., 1st paragraph). He does not teach the use of a membrane anchoring sequence in the vector.

Kim teaches a DNA vaccine vector that encodes an HIV-1 antigen and interleukin-12 (IL-12) (p. 817, 1st col., 1st paragraph). Kim further teaches that this combination results in a dramatic increase in specific cytotoxic T cell responses (p. 823, 2nd col., 2nd paragraph). Kim does not teach the use of a membrane anchoring sequence in the vector.

Finke teaches that transfection of cytokine induced killer cells with a vector encoding interleukin-7 (IL-7) results in enhanced cytolytic and proliferative capacities of these lymphocytes against HT144 tumor cells *in vitro* (p. 33, 2nd col., last paragraph). Finke does not teach the use of this vector *in vivo*, the use of a membrane anchoring sequence in the vector, nor the combination of IL-7 and an antigen.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the work of Lin with Chow, He, Kim, or Finke to produce a recombinant vector the encodes a papilloma antigen and a membrane anchoring sequence combined with an immunostimulator such as IL-2, IL-7, IL-12, or B7-1. One of ordinary skill in the art would have been motivated to combine the teachings of Lin with Chow, He, Kim, or Sharma to produce a vector that induces a more potent immune response to the papilloma antigen.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 30 containing SEQ ID NO: 1 and SEQ ID NO: 2 is free from the prior art.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael G. Penn who can normally be reached on Monday through Friday from 8:00 am to 4:30 p.m. at (703) 308-2454.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, who can normally be reached on Monday through Friday from 9:00 am to 5:30 p.m. at (703) 305-3015.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael G. Penn

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